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(54) Title: SKIN PREPARATION COMPRISING A TOCOPHEROL DERIVATIVE FOR EXTERNAL APPLICATION

(57) Abstract: The present invention relates to a skin preparation for external application, comprising a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof. The preferable tocopherol aminoalkylcarboxylate ester in the present invention is one or more compound selected from α-tocopherol derivatives, β-tocopherol derivatives, γ-tocopherol derivatives and δ-tocopherol derivatives. The present invention also relates to a cosmetic material comprising the skin preparation for external application.

DESCRIPTION

SKIN PREPARATION COMPRISING A TOCOPHEROL DERIVATIVE FOR EXTERNAL APPLICATION

This application is an application filed under 35 U.S.C. 111(a) claimng pursuant to 35 U.S.C. 119 (e) of the filing date of Provisional Application 60/359,334 on February 26, 2002, Provisional Application 60/373,579 on April 19, 2002, pursuant to 35 U.S.C. 111(b).

Technical Field

The present invention relates to a skin preparation for external application and a cosmetic material, characterized in that a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof is blended.

Background Art

Tocopherols (e.g., α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol) known as vitamin E and derivatives thereof such as tocopherol acetate and tocopherol nicotinate are known to provide efficacy and effect such as activities of antioxidation, vital membrane stabilization, immunoactivation and acceleration of blood circulation and have been long blended in medical preparations, cosmetics, samples and the like.

However, these compounds are oil-soluble and cannot be

uniformly dispersed in an aqueous solution or an emulsion. In the case of preparing a medical or cosmetic product in the solubilized or emulsion state, a nonionic surfactant is generally used to enable uniform dispersion, however, some nonionic surfactants are highly irritating or give rise to environmental pollution and therefore, in view of safety, use of the nonionic surfactant is considered undesirable and improvement is demanded in this point.

Furthermore, tocopherols in the simple form are readily oxidized and unstable and therefore, are used as an organic acid ester derivative such as acetate ester, nicotinate ester or succinate ester in many cases. In order to allow the organic acid ester derivative to exert in vivo the physiological activity as tocopherol, the ester bond moiety must be hydrolyzed by an enzyme such as esterase, however, the conversion rate of those derivatives is not sufficiently high and the effect of increasing the concentration in the tissue is low.

It is an object of the present invention to improve the solubility and emulsifiability of tocopherol in skin preparations for external application and provide a composition which undergoes efficient conversion to active tocopherol in the skin tissue.

Disclosure of the Invention

As a result of extensive investigations to overcome the above-described problems, the present inventors have found

that a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof have useful solubility and emulsifiability, and have accomplished the present invention. As used herein, "having a substituent on the N atom" means to have a substituent other than an alkylcarboxylate group on an amino group of the aminoalkylcarboxylate.

The present inventors have also found that the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof are efficiently converted to active tocopherol in skin tissue, and have accomplished the present invention.

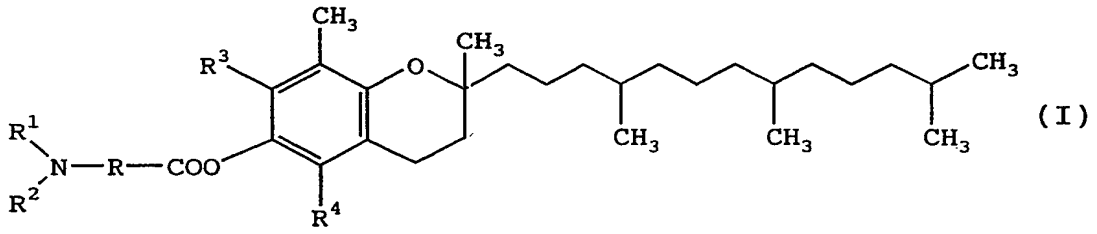
More specifically, the present invention relates to the following matters.

[1] A skin preparation for external application, comprising a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof.

[2] The skin preparation for external application as described in [1] above, wherein the tocopherol aminoalkylcarboxylate ester is one or more compound selected from α-tocopherol derivatives, β-tocopherol derivatives, γ-tocopherol derivatives and δ-tocopherol derivatives.

[3] The skin preparation for external application as described in [2] above, wherein the tocopherol amino-alkylcarboxylate ester is an α-tocopherol aminoalkyl-carboxylate ester or a γ-tocopherol aminoalkylcarboxylate ester.

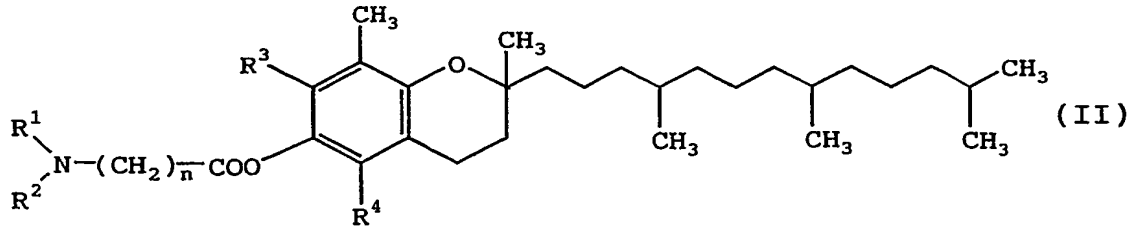
[4] The skin preparation for external application as described in any one of [1] to [3] above, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom comprises a compound represented by formula (I):



(I)

(wherein R^1 and R^2 may be the same or different and each represents a lower alkyl group or a hydrogen atom, R^3 and R^4 each represents a hydrogen atom or a methyl group and R represents a branched or linear alkylene group which may have a substituent, provided that R^1 and R^2 are not a hydrogen atom at the same time).

[5] The skin preparation for external application as described in any one of [1] to [4] above, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom comprises a compound represented by formula (II):



(II)

(wherein R^1 and R^2 may be the same or different and each

represents a lower alkyl group or a hydrogen tom, R^3 and R^4 each represents a hydrogen atom or a methyl group, and n represents an integer of 1 to 7, provided that R^1 and R^2 are not a hydrogen atom at the same time).

[6] The skin preparation for external application as described in any one of [1] to [5] above, wherein the aminoalkylcarboxylic acid of the tocopherol aminoalkyl-carboxylate ester having a substituent on the N atom is a compound selected from the group consisting of glycine, alanine, β-alanine, valine, leucine, isoleucine, phenylalanine, methionine, cysteine, serine, threonine, tyrosine, thyroxine, histidine, proline, 4-hydroxyproline, aspartic acid, glutamic acid and their N-alkyl derivatives and N,N-dialkyl derivatives.

[7] The skin preparation for external application as described in any one of [1] to [6] above, wherein the aminoalkylcarboxylic acid of the tocopherol aminoalkyl-carboxylate ester having a substituent on the N atom has a monoamino group and the monoamino groiup is a monoalkylamino group.

[8] The skin preparation for external application as described in any one of [1] to [7] above, wherein the aminoalkylcarboxylic acid of the tocopherol aminoalkyl-carboxylate ester having a substituent on the N atom has a monoamino group and the monoamino group is a dialkylamino group.

[9] The skin preparation for external application as

described in [7] above, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom is an N,N-dimethylglycine ester of tocopherol.

[10] The skin preparation for external application as described in [8] above, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom is a tocopherol sarcosine ester.

[11] The skin preparation for external application as described in any one of [1] to [10] above, wherein the salt is a hydrohalogenic acid salt.

[12] The skin preparation for external application as described in [11] above, wherein the hydrohalogenic acid is hydrochloric acid.

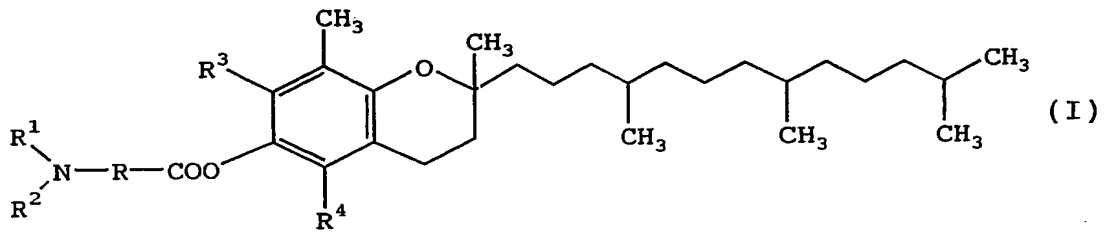
[13] The skin preparation for external application as described in any one of [1] to [12] above, wherein the content of the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof is from 0.01 to 10 mass%.

[14] A cosmetic material comprising the skin preparation for external application described in any one of [1] to [13] above.

Best Mode for Carrying Out the Invention

The tocopherol aminoalkylcarboxylate ester derivative having a substituent on the N atom and/or a salt thereof for use in the skin preparation for external application of the present invention are described below.

In the present invention, the tocopherol aminoalkyl-carboxylate ester having a substituent on the N atom is, for example, a compound represented by the following formula (I) and/or a salt thereof:



(I)

(wherein R^1 and R^2 may be the same or different and each represents a lower alkyl group or a hydrogen atom, R^3 and R^4 each represents a hydrogen atom or a methyl group and R represents a branched or linear alkylene group which may have a substituent, provided that R^1 and R^2 are not a hydrogen atom at the same time).

As seen from the formula above, the tocopherol which can be used in the present invention includes α-, β-, γ- and δ-tocopherol derivatives. Among these, preferred are α-tocopherol where R^3 and R^4 are methyl, and γ-tocopherol where R^3 is methyl and R^4 is a hydrogen atom.

These tocopherol derivatives have an asymmetric carbon atom at the 2-position of the chromanol ring and therefore, steric isomers such as d form and dl form are present. Needless to say, the present invention includes all of these isomers.

The lower alkyl group in the definition of R^1 and R^2 of formula (I) is a linear or branched alkyl group having from 1

to 6 carbon atoms and examples thereof include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl. Among these, most preferred are a methyl group and an ethyl group.

Examples of the aminoalkylcarboxylic acids constituting the tocopherol aminoalkylcarboxylate ester for use in the present invention include glycine, alanine, β-alanine, valine, leucine, isoleucine, phenylalanine, methionine, cysteine, serine, threonine, tyrosine, thyroxine, histidine, proline, 4-hydroxyproline, aspartic acid, glutamic acid and their N-alkyl derivatives and N,N-dialkyl derivatives.

Among these aminoalkylcarboxylic acids, preferred are dimethylglycine and sarcosine.

These aminoalkylcarboxylic acids may be any of D form, L form and DL form but in view of bioactivity and the like, L form or DL form is preferred.

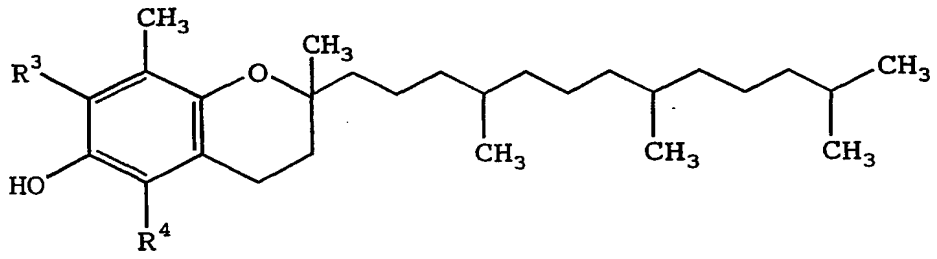
In the present invention, a salt is preferred and the salt is preferably a hydrohalogenic acid salt, more preferably an HCl salt or an HBr salt. In particular, the HCl salt is advantageous in that the solubility in water increases and due to its powder form, handling is facilitated.

The tocopherol aminoalkylcarboxylate ester derivative having a substituent on the N atom for use in the present invention may be produced by various methods, but a representative method is described below.

The production method is described by referring to the case of $R=(CH_2)_n$ (wherein n represents an integer of 1 to 7)

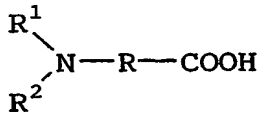
which is a preferred example.

This compound can be easily obtained by performing an esterification reaction of a tocopherol represented by the following formula (III):



(III)

(wherein R^3 and R^4 each represents a hydrogen atom or a methyl group) and any one of an aminoalkylcarboxylic acid represented by the following formula (IV):



(IV)

(wherein R^1 and R^2 may be the same or different and each represents a lower alkyl group or a hydrogen atom, and R represents a branched or linear alkylene group which may have a substituent, provided that R^1 and R^2 are not a hydrogen atom at the same time), its reactive acid derivative and a salt thereof such as hydrohalogenic acid salt, in a usual manner.

In the case of directly performing the esterification using a free aminoalkylcarboxylic acid, usually, the reaction is preferably performed in the presence of an active esterification reagent (dehydrating agent) such as dicyclohexylcarbodiimide and N,N-disuccinimide oxalate. At

this time, the solvent is most preferably pyridine.

If desired, the aminoalkylcarboxylic acid having a substituent on the N atom after the completion of reaction is preferably subjected to a treatment for removing the protective group using an aminoalkylcarboxylic acid in which the amino group is protected, for example, by an N-tert-butoxycarbonyl (BOC) group, a benzyloxycarbonyl group or a 2-nitrobenzenesulfonyl group.

In the method of using a reactive acid derivative, an acid halide, particularly acid chloride is preferably used.

In the case of producing a hydrohalogenic acid salt of a tocopherol aminoalkylcarboxylate ester, the hydrohalogenic acid salt may be produced by once producing an ester form and reacting it with a hydrohalogenic acid (gas phase or solution) in a usual manner, or a hydrohalogenic acid salt of an aminoalkylcarboxylic acid represented by formula (IV) may be previously used as a starting material.

The thus-obtained tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a hydrohalogenic acid salt thereof are excellent in the solubility and emulsifiability as compared with tocopherols in a simple form. Furthermore, when applied as a skin preparation for external application, these are readily hydrolyzed by an esterase or carboxyl esterase in the skin tissue to produce an active free tocopherol.

Therefore, the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a hydrohalogenic

acid salt thereof of the present invention can be used as an active ingredient of skin preparations for external application which are expected to have efficacy and effect such as activities of antioxidation, vital membrane stabilization, immunoactivation and acceleration of blood circulation.

The present invention relates to a skin preparation for external application where a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a hydrohalogenic acid salt thereof is blended, and the skin preparation for external application of the present invention can be used as a cosmetic material.

The cosmetic material of the present invention includes, in a wide sense, cosmetic materials which come into contact with skin on use, for example, skin milk, skin cream, foundation cream, massage cream, cleansing cream, shaving cream, cleansing foam, skin lotion, lotion, pack, shampoo, rinse, hair restorer, hair nourishment, hair dye, hair conditioner, toothpaste, gargle, permanent waving agent, ointment, bath preparation and body soap. The user may be any user irrespective of sex or age.

In the skin preparation for external application and the cosmetic material of the present invention, ingredients commonly used in skin preparations for external application can be blended within the range of not impairing the effect of the present invention. Examples thereof include chemicals described in Japanese Standards of Cosmetic Ingredients (JSCI),

2nd Edition, Annotation, compiled by Nippon Koteisho Kyokai, issued by Yakuji Nippo, Ltd. (1984), Specifications of Ingredient Other Than Those Listed in JSCI, supervised by Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), Specifications of Ingredient Other Than Those Listed in JSCI, Supplement, supervised by Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), The Comprehensive Licensing Standards of Cosmetics by Category, supervised by Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), and Kesho-hin Genryo Jiten (Handbook of Cosmetic Ingredients), Nikko Chemicals (1991).

Examples

The present invention is described in greater detail below by referring to Examples, however, the present invention is not limited to these Examples. In Examples, the amount blended is in the unit of mass%.

Example 1

Lotion 1

	Example 1
1) α-Tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20

5) Purified water	87.8

(Production Method of Example 1)

Ingredients 1) and 2) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion.

Example 2

Lotion 2

	Example 2
1) α-Tocopherol sarcosine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

(Production Method of Example 2)

Ingredients 1) and 2) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion.

Comparative Example 1

Lotion 3

	Comparative Example 1
1) Tocopherol acetate	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

(Production Method of Comparative Example 1)

Ingredients 1) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion.

(Results)

Lotion 1 obtained in Examples 1 and 2 was uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 1, uniform dissolution or dispersion could not be attained and a lotion having excellent solubility could not be obtained.

Example 3

Lotion 4

	Example 3
1) α-Tocopherol dimethylglycine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Example 3)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion.

Example 4

Lotion 5

	Example 4
1) α-Tocopherol sarcosine ester hydrochloride	0.10

2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Example 4)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion.

Comparative Example 2

Lotion 6

	Comparative Example 2
1) Tocopherol acetate	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Comparative Example 2)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion.

(Results)

Lotions 4 and 5 obtained in Examples 3 and 4 were uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 2, uniform dissolution or dispersion could not be attained, floating of oil droplets was confirmed and a lotion 6 having excellent solubility could not be obtained.

Example 5

Lotion 7

	Example 5
1) α-Tocopherol dimethylglycine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Sodium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 5)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring to 5) in which 4) was previously dissolved, to obtain the objective lotion.

Example 6

Lotion 8

	Example 6
1) α-Tocopherol sarcosine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Magnesium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 6)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring to 5) in which 4) was previously dissolved, to obtain the objective lotion.

Comparative Example 3

Lotion 9

	Comparative Example 3
1) Tocopherol acetate	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Sodium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Comparative Example 3)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring to 5) in which 4) was previously dissolved, to obtain the objective lotion.

(Results)

Lotions 7 and 8 obtained in Examples 5 and 6 were uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 3, uniform dissolution or dispersion could not be attained, floating of oil droplets was confirmed and a lotion having excellent solubility could not be obtained.

Example 7

Gel Preparation 1 for External Application

	Example 7
1) α-Tocopherol dimethylglycine ester hydrochloride	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Example 7)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation 1 for external application.

Example 8

Gel Preparation 2 for External Application

	Example 8
1) α-Tocopherol sarcosine ester hydrochloride	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Example 8)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation 2 for external application.

Comparative Example 4

Gel Preparation 3 for External Application

	Comparative Example 4
1) Tocopherol acetate	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Comparative Example 4)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation 3 for external application.

(Results)

Gel preparations 1 and 2 for external application

obtained in Examples 7 and 8 had a translucent gel appearance and exhibited good aging stability. On the other hand, in Comparative Example 4, gel was not formed.

Example 9

Milky Lotion 1

	Example 9
1) α-Tocopherol dimethylglycine ester hydrochloride	5.0
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Purified water	64.8

(Production Method of Example 9)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 5) with stirring to obtain the objective milky lotion 1.

Example 10

Milky Lotion 2

	Example 10
1) α-Tocopherol sarcosine ester hydrochloride	5.0
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Purified water	64.8

(Production Method of Example 10)

Ingredient 1) was uniformly dispersed and dissolved in

2) to 4) and this was added to 5) with stirring to obtain the objective milky lotion 2.

Comparative Example 5

Milky Lotion 3

	Comparative Example 5
1) Tocopherol acetate	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Purified water	64.8

(Production Method of Comparative Example 5)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 5) with stirring to obtain the objective milky lotion 3.

(Results)

Milky lotions 1 and 2 obtained in Examples 9 and 10 gave good feeling on use and exhibited good aging stability. On the other hand, in Comparative Example 5, emulsion was not formed and a milky lotion could not be obtained.

Example 11

Milky Lotion 4

	Example 11
1) α-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0

5) Sodium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 11)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 4.

Example 12

Milky Lotion 5

	Example 12
1) α-Tocopherol dimethylglycine ester hydrochloride	5.0
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Magnesium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 12)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 5.

Example 13

Milky Lotion 6

	Example 13
1) α-Tocopherol sarcosine ester hydrochloride	5.00
2) Propylene glycol	10.0

3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Sodium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 13)

Any one of 1) to 3) was uniformly dispersed and dissolved in 5) to 6) and thereto, 9) in which 8) was previously dissolved was added with stirring to obtain the objective milky lotion 6.

Example 14

Milky Lotion 7

	Example 14
1) α-Tocopherol sarcosine ester hydrochloride	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Magnesium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 14)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 7.

Comparative Example 6

Milky Lotion 8

	Comparative Example 6

1) Tocopherol acetate	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Sodium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Comparative Example 6)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 8.

(Results)

Milky lotions 4 to 7 obtained in Examples 11 to 14 gave good feeling on use and exhibited good aging stability. On the other hand, in Comparative Example 6, emulsion was not formed and a milky lotion could not be obtained.

Example 15

Milky Lotion 9

	Example 15
1) α-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 15)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 9.

Example 16

Milky Lotion 10

	Example 16
1) α-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Magnesium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 16)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 10.

Example 17

Milky Lotion 11

	Example 17
1) α-Tocopherol sarcosine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20

4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 17)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 6) in which 5) was previously dissolved with stirring to obtain the objective milky lotion 11.

Example 18

Milky Lotion 12

	Example 18
1) α-Tocopherol sarcosine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Magnesium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 17)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 12.

Comparative Example 7

Milky Lotion 13

	Comparative Example 7
1) Tocopherol acetate	5.00

2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Comparative Example 7)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 13.

(Results)

Milky lotions 9 to 12 obtained in Examples 15 to 18 gave good feeling on use and exhibited good aging stability. On the other hand, in the milky lotion 13 obtained in Comparative Example 7, phase separation was observed after a few days and good aging stability could not be obtained.

Example 19 and Comparative Example 8

Evaluation of Skin Penetrability

(Method)

In each of ϕ35 mm plastic Petri dishes, 1 ml of a Dulbecco's MEM medium containing 1), 2), 3) or 4) was placed and a nylon mesh and a lens paper were sequentially laid thereon. On the lens paper, a skin removed from the back of a hairless mouse was placed such that the epidermis came into contact with the lens paper. At this time, the dermis side was covered with a parafilm and thereby prevented from drying.

1) Not added

2) α-Tocopherol dimethylglycine ester hydrochloride 0.50

3) α-Tocopherol sarcosine ester hydrochloride 0.50

4) Tocopherol acetate 0.50

After the passage of 4 hours at 37°C, the skin was washed with a phosphoric acid buffer solution and homogenized. Then, the amount of α-tocopherol in the skin was measured. The determination of α-tocopherol was performed by high performance liquid chromatography.

The conditions for measurement by high performance liquid chromatography were as follows.

Column: Shodex ODSpak F-411

Temperature: 40°C

Eluent: methanol/acetonitrile = 7/3 (containing 0.02M acetic acid and 0.02M sodium acetate)

Flow rate: 0.7 ml

Detection: fluorescent, Ex: 298 nm, Em: 325 nm

(Results)

1) 10 nmol/g of skin

2) 17 nmol/g of skin

3) 20 nmol/g of skin

4) 11 nmol/g of skin

The skin treated with α-tocopherol dimethylglycine ester hydrochloride or α-tocopherol sarcosine ester hydrochloride had significant increase of the α-tocopherol amount.

Example 20 and Comparative Example 9

Conversion to α-Tocopherol in Keratinocyte of Human Epidermis

(Method)

Commercially available keratinocytes of normal human epidermis were cultured in the medium attached. The cells were harvested and spalled by freeze-thawing method. To this cell spall solution, 1), 2), 3) or 4) was added to have a final concentration of 1 mM. The resulting solution was kept at 37°C for 2 hours and then the amount of α-tocopherol liberated in the reaction solution was measured. The determination of α-tocopherol was performed by high performance liquid chromatography.

The conditions for measurement by high performance liquid chromatography were as follows.

Column:	Shodex ODSpak F-411
Temperature:	40°C
Eluent:	methanol/acetonitrile = 7/3 (containing 0.02M acetic acid and 0.02M sodium acetate)
Flow rate:	0.7 ml
Detection:	fluorescent, Ex: 298 nm, Em: 325 nm

1) Not added
2) α-Tocopherol dimethylglycine ester hydrochloride
3) α-Tocopherol sarcosine ester hydrochloride
4) Tocopherol acetate

(Results)

1) lower than detection limit

2) 6.9 nmol/ml of cell suspension

3) 26.9 nmol/ml of cell suspension

4) 0.5 nmol/ml of cell suspension

The cell spall solution in which α-tocopherol dimethylglycine ester hydrochloride or α-tocopherol sarcosine ester hydrochloride was added, had significant increase of the α-tocopherol amount.

Example 21

Lotion 10

	Example 21
1) γ-Tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

(Production Method of Example 21)

Ingredients 1) and 2) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion 10.

Example 22

Lotion 11

	Example 22
1) γ-Tocopherol sarcosine ester hydrochloride	2.00
2) Ethanol	5.00

3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

(Production Method of Example 22)

Ingredients 1) and 2) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion 11.

Comparative Example 10

Lotion 12

	Comparative Example 10
1) γ-Tocopherol	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

(Production Method of Comparative Example 10)

Ingredients 1) and 2) to 4) were uniformly dispersed and dissolved and the resulting solution was added to 5) with stirring to obtain the objective lotion 12.

(Results)

Lotions 10 and 11 obtained in Examples 21 and 22 was uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 10, uniform dissolution or dispersion could not be attained and a lotion having excellent solubility could not be obtained.

Example 23

Lotion 13

	Example 23
1) γ-Tocopherol dimethylglycine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Example 23)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion 13.

Example 24

Lotion 14

	Example 24
1) γ-Tocopherol sarcosine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Example 23)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion 14.

Comparative Example 11

Lotion 15

	Comparative Example 11

1) γ-Tocopherol	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Purified water	94.7

(Production Method of Comparative Example 11)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added to 4) with stirring to obtain the objective lotion 15.

(Results)

Lotions 13 and 14 obtained in Examples 23 and 24 were uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 11, uniform dissolution or dispersion could not be attained, floating of oil droplets was confirmed and a lotion having excellent solubility could not be obtained.

Example 25

Lotion 16

	Example 25
1) γ-Tocopherol dimethylglycine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Sodium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 25)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring

to 5) in which 4) was previously dissolved, to obtain the objective lotion 16.

Example 26

Lotion 17

	Example 26
1) γ-Tocopherol dimethylglycine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Magnesium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 26)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring to 5) in which 4) was previously dissolved, to obtain the objective lotion 17.

Example 27

Lotion 18

	Example 27
1) γ-Tocopherol sarcosine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Sodium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 27)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring

to 5) in which 4) was previously dissolved, to obtain the objective lotion 18.

Example 28

Lotion 19

	Example 28
1) γ-Tocopherol sarcosine ester hydrochloride	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Magnesium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Example 28)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring to 5) in which 4) was previously dissolved, to obtain the objective lotion 19.

Comparative Example 12

Lotion 20

	Comparative Example 12
1) γ-Tocopherol	0.10
2) Propylene glycol	5.00
3) Methyl parahydroxybenzoate	0.20
4) Sodium ascorbyl phosphate	3.00
5) Purified water	91.7

(Production Method of Comparative Example 12)

Ingredients 1), 2) and 3) were uniformly dispersed and dissolved and the resulting solution was added with stirring

to 5) in which 4) was previously dissolved, to obtain the objective lotion 20.

(Results)

Lotions 16 to 19 obtained in Examples 25 to 28 were uniformly dissolved and exhibited good aging stability. On the other hand, in Comparative Example 12, uniform dissolution or dispersion could not be attained, floating of oil droplets was confirmed and a lotion having excellent solubility could not be obtained.

Example 29

Gel Preparation 4 for External Application

	Example 29
1) γ-Tocopherol dimethylglycine ester hydrochloride	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Example 28)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation 4 for external application.

Example 30

Gel Preparation 5 for External Application

	Example 30
1) γ-Tocopherol sarcosine ester hydrochloride	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Example 30)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation 5 for external application.

Comparative Example 13

Gel Preparation 6 for External Application

	Comparative Example 13
1) γ-Tocopherol	10.0
2) Glycerin	20.0
3) Octyldodecyl myristate	70.0

(Production Method of Comparative Example 13)

Ingredient 1) was uniformly dispersed in 2) and the resulting dispersion was added to 3) with stirring to obtain the objective gel preparation for external application.

(Results)

Gel preparations 4 and 5 for external application obtained in Examples 29 and 30 had a translucent gel appearance and exhibited good aging stability. On the other hand, in Comparative Example 13, gel was not formed.

Example 31

Milky Lotion 14

	Example 31
1) γ-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0

5) Purified water	64.8

(Production Method of Example 31)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 5) with stirring to obtain the objective milky lotion 14.

Example 32

Milky Lotion 15

	Example 32
1) γ-Tocopherol sarcosine ester hydrochloride	5.0
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Purified water	64.8

(Production Method of Example 32)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 5) was added with stirring to obtain the objective milky lotion 15.

Comparative Example 14

Milky Lotion 16

	Comparative Example 14
1) γ-Tocopherol	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Purified water	64.8

(Production Method of Comparative Example 14)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added to 5) was added with stirring to obtain the objective milky lotion 16.

(Results)

Milky lotions 14 and 15 obtained in Examples 31 and 32 gave good feeling on use and exhibited good aging stability. On the other hand, in Comparative Example 14, emulsion was not formed and a milky lotion could not be obtained.

Example 33

Milky Lotion 17

	Example 33
1) γ-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Sodium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 33)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 17.

Example 34

Milky Lotion 18

	Example 34

1)	γ-Tocopherol dimethylglycine ester hydrochloride	5.00
2)	Propylene glycol	10.0
3)	Methyl parahydroxybenzoate	0.20
4)	Methylphenylpolysiloxane	20.0
5)	Magnesium ascorbyl phosphate	3.00
6)	Purified water	61.8

(Production Method of Example 34)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 18.

Example 35

Milky Lotion 19

		Example 35
1)	γ-Tocopherol sarcosine ester hydrochloride	5.00
2)	Propylene glycol	10.0
3)	Methyl parahydroxybenzoate	0.20
4)	Methylphenylpolysiloxane	20.0
5)	Sodium ascorbyl phosphate	3.00
6)	Purified water	61.8

(Production Method of Example 35)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 19.

Example 36

Milky Lotion 20

	Example 36
1) γ-Tocopherol sarcosine ester hydrochloride	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Magnesium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Example 36)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5) was previously dissolved to obtain the objective milky lotion 20.

Comparative Example 15

Milky Lotion 21

	Comparative Example 15
1) γ-Tocopherol	5.00
2) Propylene glycol	10.0
3) Methyl parahydroxybenzoate	0.20
4) Methylphenylpolysiloxane	20.0
5) Sodium ascorbyl phosphate	3.00
6) Purified water	61.8

(Production Method of Comparative Example 15)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and this was added, with stirring, to 6) in which 5)

was previously dissolved to obtain the objective milky lotion 21.

(Results)

Milky lotions 17 to 20 obtained in Examples 33 to 36 gave good feeling on use and exhibited good aging stability. On the other hand, in Comparative Example 15, emulsion was not formed and a milky lotion could not be obtained.

Example 37

Milky Lotion 22

	Example 37
1) γ-Tocopherol dimethylglycine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 37)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 22.

Example 38

Milky Lotion 23

	Example 38
1) γ-Tocopherol dimethylglycine ester hydrochloride	5.00

2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Magnesium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 38)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 23.

Example 39

Milky Lotion 24

	Example 39
1) γ-Tocopherol sarcosine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 39)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 24.

Example 40

Milky Lotion 25

	Example 40
1) γ-Tocopherol sarcosine ester hydrochloride	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Magnesium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Example 40)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring to 6) in which 5) was previously dissolved, to obtain the objective milky lotion 25.

Comparative Example 16

Milky Lotion 26

	Comparative Example 16
1) γ-Tocopherol	5.00
2) Hydrogenated soybean phospholipid	10.0
3) Methyl parahydroxybenzoate	0.20
4) 2-Ethylhexanoic acid triglyceride	20.0
5) Sodium ascorbyl phosphate	2.00
6) Purified water	61.8

(Production Method of Comparative Example 16)

Ingredient 1) was uniformly dispersed and dissolved in 2) to 4) and the resulting solution was added with stirring

to 6) in which 5) was previously dissolved, to obtain the milky lotion 26.

(Results)

Milky lotions 22 to 25 obtained in Examples 37 to 40 gave good feeling on use and exhibited good aging stability. On the other hand, in the milky lotion obtained in Comparative Example 16, phase separation was observed after a few days and good aging stability could not be obtained.

Example 41 and Comparative Example 17

Evaluation of Skin Penetrability

(Method)

In each of ϕ35 mm plastic Petri dishes, 1 ml of a Dulbecco's MEM medium containing 1), 2) or 3) was placed and a nylon mesh and a lens paper were sequentially laid thereon. On the lens paper, a skin removed from the back of a hairless mouse was placed such that the epidermis came into contact with the lens paper. At this time, the dermis side was covered with a parafilm and thereby prevented from drying.

1) Not added

2) γ-Tocopherol dimethylglycine ester hydrochloride 0.50

3) γ-Tocopherol sarcosine ester hydrochloride 0.50

After the passage of 4 hours at 37°C, the skin was washed with a phosphoric acid buffer solution and homogenized. Then, the amount of γ-tocopherol in the skin was measured. The determination of γ-tocopherol was performed by high performance liquid chromatography.

The conditions for measurement by high performance liquid chromatography were as follows.

Column: Shodex ODSpak F-411

Temperature: 40°C

Eluent: methanol/acetonitrile = 7/3 (containing 0.02M acetic acid and 0.02M sodium acetate)

Flow rate: 0.7 ml

Detection: fluorescent, Ex: 298 nm, Em: 325 nm

(Results)

1) lower than detection limit

2) 20 nmol/g of skin

3) 21 nmol/g of skin

The skin treated with γ-tocopherol dimethylglycine ester hydrochloride or γ-tocopherol sarcosine ester hydrochloride had significant increase of the γ-tocopherol amount.

Example 42 and Comparative Example 18

Conversion to γ-Tocopherol in Keratinocyte of Human Epidermis

(Method)

Commercially available keratinocytes of normal human epidermis were cultured in the medium attached. The cells were harvested and spalled by freeze-thawing method. To this cell spall solution, 1), 2) or 3) was added to have a final concentration of 1 mM. The resulting solution was kept at 37°C for 2 hours and then the amount of γ-tocopherol liberated in the reaction solution was measured. The

determination of γ-tocopherol was performed by high performance liquid chromatography.

The conditions for measurement by high performance liquid chromatography were as follows.

Column: Shodex ODSpak F-411

Temperature: 40°C

Eluent: methanol/acetonitrile = 7/3 (containing 0.02M acetic acid and 0.02M sodium acetate)

Flow rate: 0.7 ml

Detection: fluorescent, Ex: 298 nm, Em: 325 nm

1) Not added

2) γ-Tocopherol dimethylglycine ester hydrochloride

3) γ-Tocopherol sarcosine ester hydrochloride

(Results)

1) lower than detection limit

2) 28.1 nmol/ml of cell suspension

3) 30.3 nmol/ml of cell suspension

The cell spall solution in which γ-tocopherol dimethylglycine ester hydrochloride or γ-tocopherol sarcosine ester hydrochloride was added, had significant increase of the γ-tocopherol amount.

Permeability of three dimensional model of human skin tissue and tocopherol conversion

40 μL of a 1 % solution of the below test substances 1) to 7) dissolved or dispersed in Dulbecco's PBS (-) were applied onto the tissue surface of a three dimensional model of human skin tissue (TESTSKIN™ LSD-d, Toyobo K. K.) and were cultured at 37ºC under 5% CO_2 for 6 hours. After this, the solutions of the test substances were removed by aspiration and sampling was carried out.

The sample model skin was washed with Dulbecco's PBS (-) and the tissue surfaces onto which the test substances were applied were punched out with a ϕ 6 mm punch, and were homogenated in a HEPES buffer solution (pH 7.2), and quantitative analysis of the α-tocopherol and γ-tocopherol were carried out by high speed liquid chromatography. Quantitative analysis of the amount of protein in the model skin was carried out according to the Lowry method.

1) α-tocopherol dimethylglycine ester hydrochloride
2) α-tocopherol sarcosine ester hydrochloride
3) α-tocopherol glycine ester
4) γ-tocopherol dimethylglycine ester hydrochloride
5) γ-tocopherol sarcosine ester hydrochloride
6) γ-tocopherol glycine ester
7) tocopherol acetate

The high speed liquid chromatography measurement conditions were as described below.

Column: Shodex ODSpak F-411

Temperature: 40ºC

Eluant: methanol/acetonitrile = 7/3 (including 0.02 M acetic acid, 0.02 M sodium acetate)

Flow rate: 0.7 ml

Detection: fluorescence, Ex 298 mm, Em 325 mm

The amounts of α-tocopherol and γ-tocopherol for the samples processed with each test substance were as follows.

1) 2.8 nmol/mg protein (the amount of α-tocopherol)

2) 3.9 nmol/mg protein (the amount of α-tocopherol)

3) 1.2 nmol/mg protein (the amount of α-tocopherol)

4) 4.7 nmol/mg protein (the amount of γ-tocopherol)

5) 5.5 nmol/mg protein (the amount of γ-tocopherol)

6) 1.5 nmol/mg protein (the amount of γ-tocopherol)

7) 1.0 nmol/mg protein (the amount of α-tocopherol)

For the processes carried out using α-tocopherol dimethylglycine ester hydrochloride, α-tocopherol sarcosine

ester hydrochloride, γ- tocopherol dimethylglycine ester hydrochloride, and γ-tocopherol sarcosine ester hydrochloride, the level of tocopherol was significantly increased.

Industrial Applicability of the Invention

The skin preparation for external application of the present invention comprising a tocopherol aminoalkyl-carboxylate ester having a substituent on the N atom and/or a salt thereof is favored with improved solubility and emulsifiability of tocopherol and efficient conversion to active tocopherol in skin tissue and therefore, can be applied over a wide range such as skin preparations for external application and cosmetic materials.

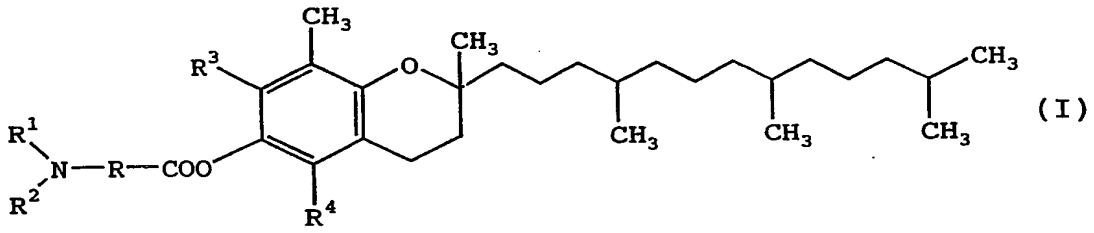
Claims

1. A skin preparation for external application, comprising a tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof.

2. The skin preparation for external application according to claim 1, wherein the tocopherol aminoalkylcarboxylate ester is one or more compound selected from α-tocopherol derivatives, β-tocopherol derivatives, γ-tocopherol derivatives and δ-tocopherol derivatives.

3. The skin preparation for external application according to claim 2, wherein the tocopherol amino-alkylcarboxylate ester is an α-tocopherol aminoalkyl-carboxylate ester or a γ-tocopherol aminoalkylcarboxylate ester.

4. The skin preparation for external application according to claim 1, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom comprises a compound represented by formula (I):

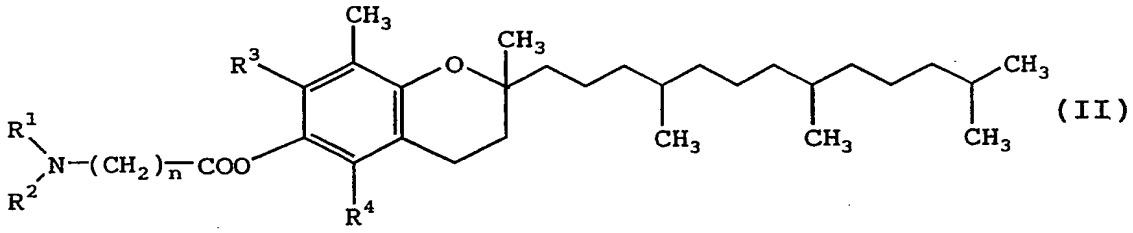


(I)

(wherein R^1 and R^2 may be the same or different and each represents a lower alkyl group or a hydrogen atom, R^3 and R^4 each represents a hydrogen atom or a methyl group and R represents a branched or linear alkylene group which may have

a substituent, provided that R^1 and R^2 are not a hydrogen atom at the same time).

5. The skin preparation for external application according to claim 4, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom comprises a compound represented by formula (II):



(II)

(wherein R^1 and R^2 may be the same or different and each represents a lower alkyl group or a hydrogen tom, R^3 and R^4 each represents a hydrogen atom or a methyl group, and n represents an integer of 1 to 7, provided that R^1 and R^2 are not a hydrogen atom at the same time).

6. The skin preparation for external application according to claim 4, wherein the aminoalkylcarboxylic acid of the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom is a compound selected from the group consisting of glycine, alanine, β-alanine, valine, leucine, isoleucine, phenylalanine, methionine, cysteine, serine, threonine, tyrosine, thyroxine, histidine, proline, 4-hydroxyproline, aspartic acid, glutamic acid and their N-alkyl derivatives and N,N-dialkyl derivatives.

7. The skin preparation for external application according to claim 1, wherein the aminoalkylcarboxylic acid

of the tocopherol aminoalkyl- carboxylate ester having a substituent on the N atom has a monoamino group and the monoamino group is a monoalkylamino group.

8. The skin preparation for external application according to claim 1, wherein the aminoalkylcarboxylic acid of the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom has a monoamino group and the monoamino group is a dialkylamino group.

9. The skin preparation for external application according to claim 7, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom is an N,N-dimethylglycine ester of tocopherol.

10. The skin preparation for external application according to claim 8, wherein the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom is a tocopherol sarcosine ester.

11. The skin preparation for external application according to claim 1, wherein the salt is a hydrohalogenic acid salt.

12. The skin preparation for external application according to claim 11, wherein the hydrohalogenic acid is hydrochloric acid.

13. The skin preparation for external application according to any one of the claims 1 to 12, wherein the content of the tocopherol aminoalkylcarboxylate ester having a substituent on the N atom and/or a salt thereof is from 0.01 to 10 mass%.

14. A cosmetic material comprising the skin preparation for external application according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT 02/11152

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K31/355

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 008, no. 085 (C-219), 18 April 1984 (1984-04-18) -& JP 59 007112 A (SHISEIDO KK), 14 January 1984 (1984-01-14) abstract; examples 1-5	1-14
X	PATENT ABSTRACTS OF JAPAN vol. 008, no. 046 (C-212), 29 February 1984 (1984-02-29) -& JP 58 203982 A (SHISEIDO KK), 28 November 1983 (1983-11-28) cited in the application abstract	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2003	06/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Vayssié, S

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INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]P 02/11152

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JIRO TAKATA ET AL: "PRODRUGS OF VITAMIN E.1" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 84, no. 1, 1995, pages 96-100, XP002092803 ISSN: 0022-3549 Paragraphs "Water solubility of the esters", "Water solubility" and "Hydrolytic studies"; chart 1 abstract; tables 1,2 ---	1-14
X	PATENT ABSTRACTS OF JAPAN vol. 014, no. 397 (C-0752), 28 August 1990 (1990-08-28) -& JP 02 149576 A (EISAI CO LTD), 8 June 1990 (1990-06-08) abstract; tables 1-1,1-2 ---	1-14
X	PATENT ABSTRACTS OF JAPAN vol. 014, no. 397 (C-0752), 28 August 1990 (1990-08-28) -& JP 02 149577 A (EISAI CO LTD), 8 June 1990 (1990-06-08) abstract; table 1 ---	1-14
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 362 (C-625), 14 August 1989 (1989-08-14) -& JP 01 121285 A (EISAI CO LTD), 12 May 1989 (1989-05-12) abstract; tables 1,4 ---	1-14
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 362 (C-625), 14 August 1989 (1989-08-14) -& JP 01 121284 A (EISAI CO LTD), 12 May 1989 (1989-05-12) abstract; table 1 ---	1-14
X	US 2 988 553 A (HANS-WALTER VOIGTLANDER ET AL) 13 June 1961 (1961-06-13) column 1, line 36; claims 1-3,5,7 ---	1-14

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INTERNATIONAL SEARCH REPORT

Inte[redacted]onal Application No
PC[redacted] 02/11152

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1997 TAKATA JIRO ET AL: "Water-soluble prodrug of vitamin E for parenteral use and its effect on endotoxin induced liver toxicity." Database accession no. PREV199799511062 XP002230111 abstract & BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 20, no. 2, 1997, pages 204-209, ISSN: 0918-6158	1-14
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 1999 (1999-07) NAGATA YOSHIKO ET AL: "Effects of a water-soluble prodrug of vitamin E on doxorubicin-induced toxicity in mice." Database accession no. PREV199900492534 XP002230112 abstract & BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 22, no. 7, July 1999 (1999-07), pages 698-702, ISSN: 0918-6158	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC[redacted] 02/11152

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JP 58203982	A	28-11-1983	NONE	
JP 02149576	A	08-06-1990	NONE	
JP 02149577	A	08-06-1990	NONE	
JP 01121285	A	12-05-1989	NONE	
JP 01121284	A	12-05-1989	NONE	
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